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CLINICAL REVIEW

Hypertension and sleep: Overview of a tight relationship

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SUMMARY

Autonomic cardiovascular control changes across sleep stages. Thus, blood pressure (BP), heart rate and peripheral vascular resistance progressively decrease in non-rapid eye movement sleep. Any deterioration in sleep quality or quantity may be associated with an increase in nocturnal BP which could participate in the development or poor control of hypertension. In the present report, sleep problems/disorders, which impact either the quality or quantity of sleep, are reviewed for their interaction with BP regulation and their potential association with prevalent or incident hypertension. Obstructive sleep apnea syndrome, sleep duration/deprivation, insomnia, restless legs syndrome and narcolepsy are successively reviewed. Obstructive sleep apnea is clearly associated with the development of hypertension that is only slightly reduced by continuous positive airway pressure treatment. Shorter and longer sleep durations are associated with prevalent or incident hypertension but age, gender, environmental exposures and ethnic differences are clear confounders. Insomnia with objective short sleep duration, restless legs syndrome and narcolepsy may impact BP control, needing additional studies to establish their impact in the development of permanent hypertension. Addressing sleep disorders or sleep habits seems a relevant issue when considering the risk of developing hypertension or the control of pre-existent hypertension. Combined sleep problems may have potential synergistic deleterious effects.

Introduction

Hypertension affects about 26.4% of the adult population worldwide. It ranks as the leading chronic risk factor for mortality, accounting for 13.5% of all deaths. Moreover, its prevalence is projected to grow and hypertension is expected to affect more than 1.5 billion people by 2025. Half of all strokes and ischemic heart disease events are attributable to high blood pressure (BP) [1,2]. BP values are normally distributed in the population and there is no natural threshold above which "hypertension" definitively exists and below which it does not. The risk associated with raised BP is continuous from as low as 115/75 mmHg, and the number of cardiovascular events doubles with each 20 mmHg increase for systolic or 10 mmHg increase for diastolic BP [3]. Nevertheless, certain definitions are used in the literature as well as in clinical practice in an effort to clarify the disease specificity/severity. According to the seventh report of the Joint National Committee [4], when BP is elevated above normal, but not to the level considered as hypertension, it is called "prehypertension". Prehypertension is BP values with a systolic BP from 120 to 139 mmHg or a diastolic BP from 80 to 89 mmHg. Values greater than or equal to 140/90 mmHg are considered as "hypertension" [3]. A normal BP profile is also characterized by a 10% fall in mean systolic BP values whilst sleeping compared to when awake, which is defined as the normal "dipping pattern" of BP at night. Patients are considered as "non-dippers" if they have a day–night systolic BP fall less than 10%; as "reverse dippers" if their night-time BP values exceed those of daytime, while "extreme dippers" present with a nocturnal BP fall of more than 20%. It is of note that there is increasing evidence that the mean nocturnal BP level is a major indicator of cardiovascular morbidity and mortality irrespective of the 24-h BP levels [5]. In this review we will see that sleep and sleep disorders can impact BP values and profile throughout 24 h.

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Abbreviations

ABPM	ambulatory blood pressure monitoring
ACTH	adrenocorticotrophic hormone
BP	blood pressure
BMI	body mass index
CARDIA	coronary artery risk development in young adults
CI	confidence interval
CPAP	continuous positive airway pressure
HPA	hypothalamus pituitary axis
PLMs	periodic limb movements in sleep
MADs	mandibular advancement devices
MSNA	muscle sympathetic nerve activity
NC	narcolepsy–cataplexy
NHNES	national health and nutrition examination survey
NREM	non-rapid eye movement sleep
OSA	obstructive sleep apnea
REM	rapid eye movement
RLS	restless legs syndrome
SHHS	sleep heart health study

Normal sleep architecture consists of four to five sleep cycles of approximately 90 min duration ach, with a cyclic alternation between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep (Fig. 1A). NREM sleep is prominent at the beginning of the night whereas the duration of REM sleep increases during the last sleep cycles. The cardiovascular system is markedly affected by normal sleep with differential autonomic regulation during the different sleep stages [6,7]. Sympathetic nerve activity to the vasculature continuously decreases with the progressive deepening of NREM sleep [8–10]. Using heart rate variability analysis, it has been demonstrated that NREM sleep is indeed characterized by vagal parasympathetic predominance, with a decline in sympathetic activity that is most marked in slow-wave sleep (Fig. 1A). As a consequence, BP and heart rate decrease throughout NREM sleep, particularly during slow-wave sleep. This corresponds to the nocturnal dipping pattern of BP. During the night, normal individuals did not exhibit significant changes in cardiac output and the nocturnal fall in arterial pressure is actually the result of a decrease in total peripheral vascular resistance. Compared with when awake, in REM sleep sympathetic activity increases significantly and is highly variable (Fig. 1B). Particularly during the phasic component of REM, BP is highly changeable and approaches wakefulness levels. Baroreflex sensitivity increases during sleep but is more effective in buffering increases in BP during REM episodes occurring at the end of the sleep period, than earlier in the night (Fig. 1C). Such a physiological setting permits the s hypothesis that the regulation of nocturnal BP could be linked to sleep characteristics. Thus, sleep problems could be involved in the pathogenesis of non-dipping, prehypertension and subsequently in hypertension. Any disturbance in sleep quantity or quality, both explained either by delirious sleep habits or sleep disorders may contribute to the development of hypertension or an increase in its severity.

In the present work, we will successively address different sleep disorders and sleep habits reviewing their potential association with nocturnal BP control and hypertension.

Obstructive sleep apnea syndrome

Obstructive sleep apnea (OSA) is now recognized as a risk factor for the development of hypertension in European and US international guidelines. OSA and hypertension are linked in a dose–response fashion. This is true even when the usual confounding factors such as age, alcohol and/or tobacco consumption and body mass index are taken into account [11]. In a large prospective observational cohort followed for more than 12 y, it has been shown that compared with controls, the adjusted hazard ratios for incident hypertension were greatest among patients with severe OSA who declined continuous positive airway pressure (CPAP therapy) (1.96; 95% confidence interval (CI), 1.44–2.66), and among those non adherent to CPAP therapy (1.78; 95% CI, 1.23–2.58), whereas the hazard ratio was lower in patients with OSA who were treated with CPAP therapy more than 4 h per night (0.71; 95% CI, 0.53–0.94) [12]. OSA-related hypertension has several characteristics: it is commonly predominately diastolic and nocturnal leading frequently to masked hypertension and non-dipper status (Fig. 2 B_3) [13]. In diastolic hypertension the main mechanism for BP elevation is the increase in vascular resistance owing to sympathetic activation. Due to its nocturnal predominance, OSA patients are at high risk of presenting masked hypertension, i.e. normal clinic BP but elevated BP when 24-h ambulatory blood pressure monitoring (ABPM) is used. Baguet et al. [14] found that in 130 patients with newly diagnosed OSA and without cardiovascular history, the prevalence of hypertension was 35.4% and 30.0% of the patients presented with masked hypertension. Moreover, it has been recently reported that neither clinic BP measurement (in the physician's office), nor home self-BP measurements (three morning and three evening BP measurements made by the patients at home) were sufficient to detect masked hypertension in OSA patients, justifying 24-h ABPM as the gold-standard to detect abnormal BP in OSA patients [15]. In addition, OSA is by far the leading cause of refractory hypertension [16,17], and should be systematically investigated in this situation.

Regarding the specific association between sleep apnea and hypertension according to age; sleep apnea in children has been shown to impact BP, independent of age, sex, race, body mass index or waist circumference [18]. In children this association also has an impact on left ventricular remodeling [19]. Primary snoring is a clinical symptom that may lead to the diagnosis of sleep breathing disorders in children; however in the current literature its independent association with an increase in BP is disputed [20,21]. The strength of the association between sleep apnea and BP decreases with age [22]. In the elderly, sleep fragmentation due to other causes also contributes to poor BP control, independently of sleep apnea [23]. Longitudinal follow-up studies on large community-based cohorts [24] or sleep clinic based cohorts [25] reveal that the risks of "all-cause" mortality and cardiovascular mortality linearly increase with the severity of sleep apnea, independently of major confounders. Lavie et al. [26] initially proposed that sleep apnea-related mortality decreased with age such that only patients younger than 50 showed excess mortality. These results were later confirmed by Rich et al. [27]. Conversely, recent studies have shown an increased mortality rate in elderly patients with severe sleep apnea [28], particularly in OSA [29].

Three meta-analyses derived from 19 randomized controlled trials have demonstrated that continuous positive airway pressure (CPAP), the first-line therapy for moderate to severe OSA syndrome, reduces the 24-h mean BP by approximately 2 mmHg (pooled estimated effect). Haentjens et al. [30] looked at 12 studies assessing CPAP vs. placebo (sham-CPAP or pills), in a total of 512 patients. However, some of the studies included in the meta-analysis excluded hypertensive patients whilst others included only hypertensive patients. Furthermore, the presence of an anti-hypertensive treatment was not consistent. Nevertheless, they concluded that CPAP therapy induces a low (−1.69 mmHg) but significant reduction in mean 24-h BP. This BP reduction was of

greater amplitude in patients with severe OSA and in patients who complied with CPAP therapy. Recent studies are concordant, suggesting that CPAP adherence for over 5.5 h/night is required to obtain the greatest reduction in BP [31,32]. Bazzano et al. [33] analyzed data from 16 placebo-controlled studies (a total of 818 OSA patients) on the effect of CPAP treatment lasting over at least two weeks on BP. The mean BP reduction with CPAP treatment vs. placebo was −2.46 mmHg (95% CI: −4.31 to −0.62) for systolic BP and −1.83 mmHg (95% CI: −3.05 to −0.61) for diastolic BP. The studies included in the meta-analysis differed in terms of the type of control treatment (eight studies used sham-CPAP, four provided a placebo in the form of a pill and four usual care alone) and the outcome measure (ABPM or clinic BP). A greater reduction in BP was associated with higher baseline BP levels, higher body mass index and more severe OSA. Mandibular advancement devices (MADs) are the only alternative treatment to CPAP. There is a scarcity of available data on the effectiveness of MADs in lowering BP in OSA patients. A significant reduction in 24-h diastolic BP with MADs compared to an inactive oral appliance has been reported with the extent BP decrease similar to that achieved with CPAP [34].Nonetheless, Phillips et al. recently reported a randomized trial comparing the effects of one-month CPAP vs. MADs on the 24 h-BP profile. Neither CPAP, nor MADs achieved a significant reduction in BP, without any difference between them [35].

Overall, the impact of CPAP in reducing BP is relatively modest. However, among patients treated for hypertension, a 1–2 mmHg mean decrease in BP is already associated with reduced risk of stroke or major cardiovascular events [36,37]. Furthermore, some specific populations having high cardiovascular risk, such as patients with resistant hypertension, exhibit greater BP reductions in response to CPAP therapy [38] and one might expect a greater benefit on long term outcomes in these subgroups. Nevertheless, the efficacy of CPAP should be put in a realistic perspective compared to the rigorous effects obtained with weight loss or exercise to reduce BP [39–41].

What is the role of sleep quantity?

Sleep deprivation

Studies of subjects experiencing short term sleep deprivation have demonstrated alterations in heart rate and BP. Lusardi et al. [42] included 18 healthy young men and women, in a cross-sectional study with two 24 h-ABPM, one week apart. During one night, subjects were asked to sleep their usual 8 h of sleep (sleep time: 21:00 h–7:00 h) whereas they were deprived of the first part of sleep time during the other night (sleep time: 02:30 h–07:00 h, about 43% of the total amount). Compared to usual sleep duration,

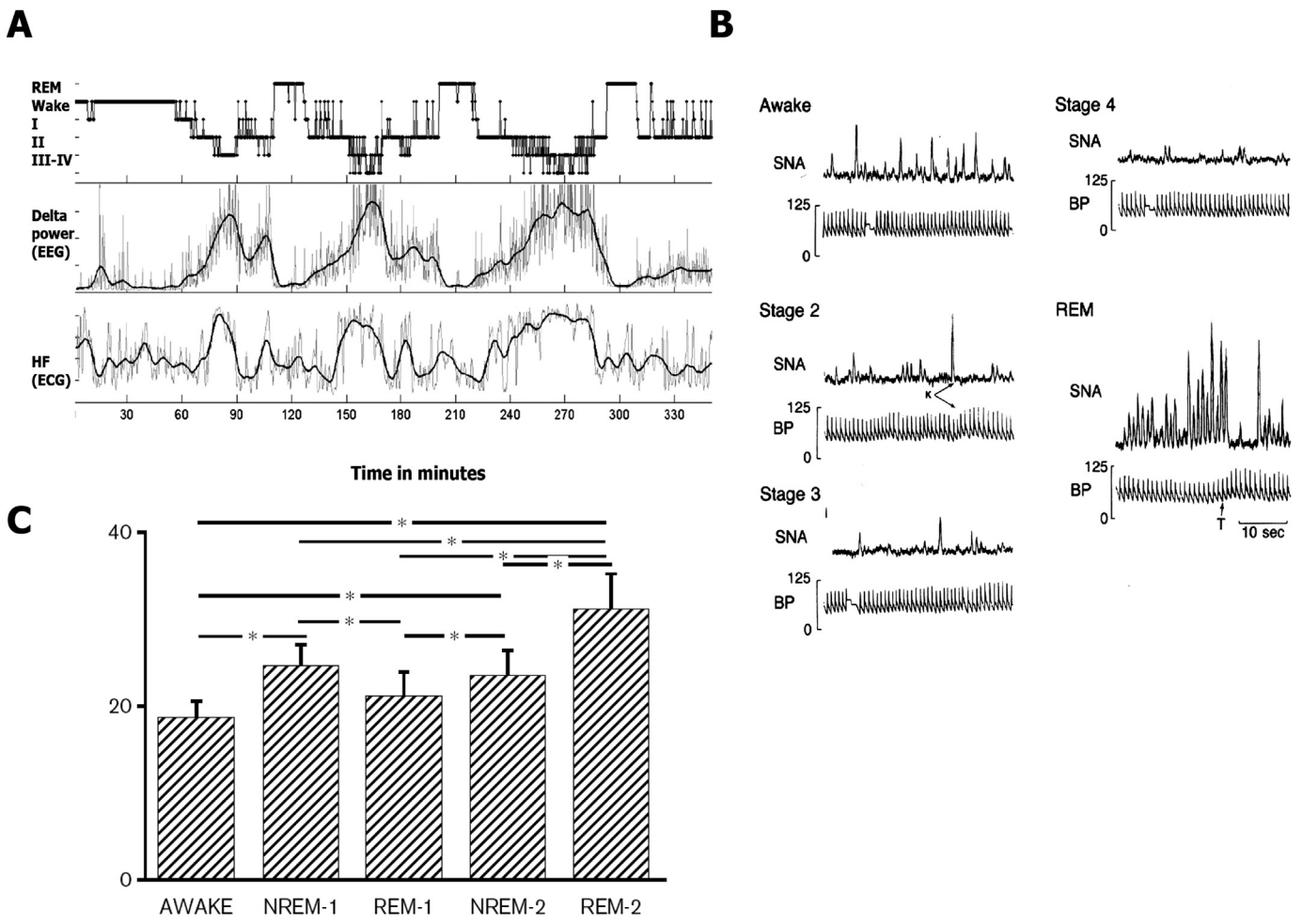

Fig. 1. Cardiovascular control during sleep. A – Normal sleep architecture and associated changes in autonomic tone. Using heart rate variability analysis, it has been demonstrated that vagal activity predominates during non-rapid eye movement (NREM) sleep (Modified From Jurysta et al. [107]). B – Variations in sympathetic activity across sleep stages as measured by muscle sympathetic nerve activity (MSNA) (Modified from Somers VK et al. [9]). C – Baroreflex sensitivity increases during sleep but is more effective in buffering increased blood pressure during rapid eye movement (REM) episodes occurring at the end of the sleep period, than earlier in the night (Modified from Legramente J et al. [108]).

the night of restricted sleep was associated with an increase in systolic BP, diastolic BP and heart rate between 21:00 h and 02:00 h as well as during the morning after 07:00 h. Tochikubo et al. [43] performed 24 h-ABPM on 18 men submitted to extensive overtime work. 24 h-ABPM was done throughout a normal workday (mean period of sleep of 8 h) and throughout a day with reduced sleep (mean period of sleep of 3.6 h). Systolic, diastolic BP and heart rate increased the day after a sleep-deprived night compared with the day after a normal sleep, as well as the urinary excretion of norepinephrine. Thus, short term sleep deprivation seems to be associated with increased BP and heart rate through the activation of the sympathetic system. Similar results were found in 36 moderately hypertensive but untreated subjects [44]. Likewise; an increase in sympathetic activation was also found by Dettoni et al. [45] in a recent study on 13 healthy Caucasian men. These men spent five nights at home with unrestricted sleep followed, after two washout nights in a cross-over design, by five nights of at home sleep restriction (−1.5 h per night). This moderate sleep deprivation did not change office measurements of resting heart rate, systolic and diastolic BP. However, even the moderate sleep deprivation was associated with a significant increase in plasma norepinephrine levels. Furthermore, important changes were observed in heart rate and BP variability with sleep pattern modifications. Thus, even a relatively small degree of sleep deprivation has been associated with a significant increase in sympathetic activation and a decrease in parasympathetic modulation of cardiac autonomic balance. Such modifications are believed to result from a reduction of NREM-sleep compared to REM-sleep. Accordingly, healthy subjects selectively deprived of slow wave sleep by electroencephalographic-guided acoustic arousal, exhibited a significantly attenuated dip in mean arterial BP g during the NREM-dominated first half of the night, but not during the REM-dominated second half of sleep (Fig. 2B1) [10]. Conversely, several studies of total sleep deprivation found increases in BP but with a reduction in resting muscle sympathetic nerve activity (MSNA) [46–48]. In presence of a reduction of MSNA, the increase in resting BP was attributed to a resetting of the sympathetic arterial baroreflex. Of note, sleep deprivation was found to increase BP similarly in men and women but only men demonstrated altered resting MSNA [48]. While the overall evidence supports an increase in nighttime and eventually daytime BP as a result of short term sleep deprivation, Pagani et al. [49] found no change in BP after one night of total sleep deprivation in 12 healthy men and 12 healthy women.

Sleep duration

Sleep duration has decreased in the general population over the last 30 years [50]. In the US, the National Sleep Foundation reported a decrease in mean sleep duration from 9 h/per night in 1910 to 7.5 h in 1975 and 6.8 h in 2005. Two major community-based

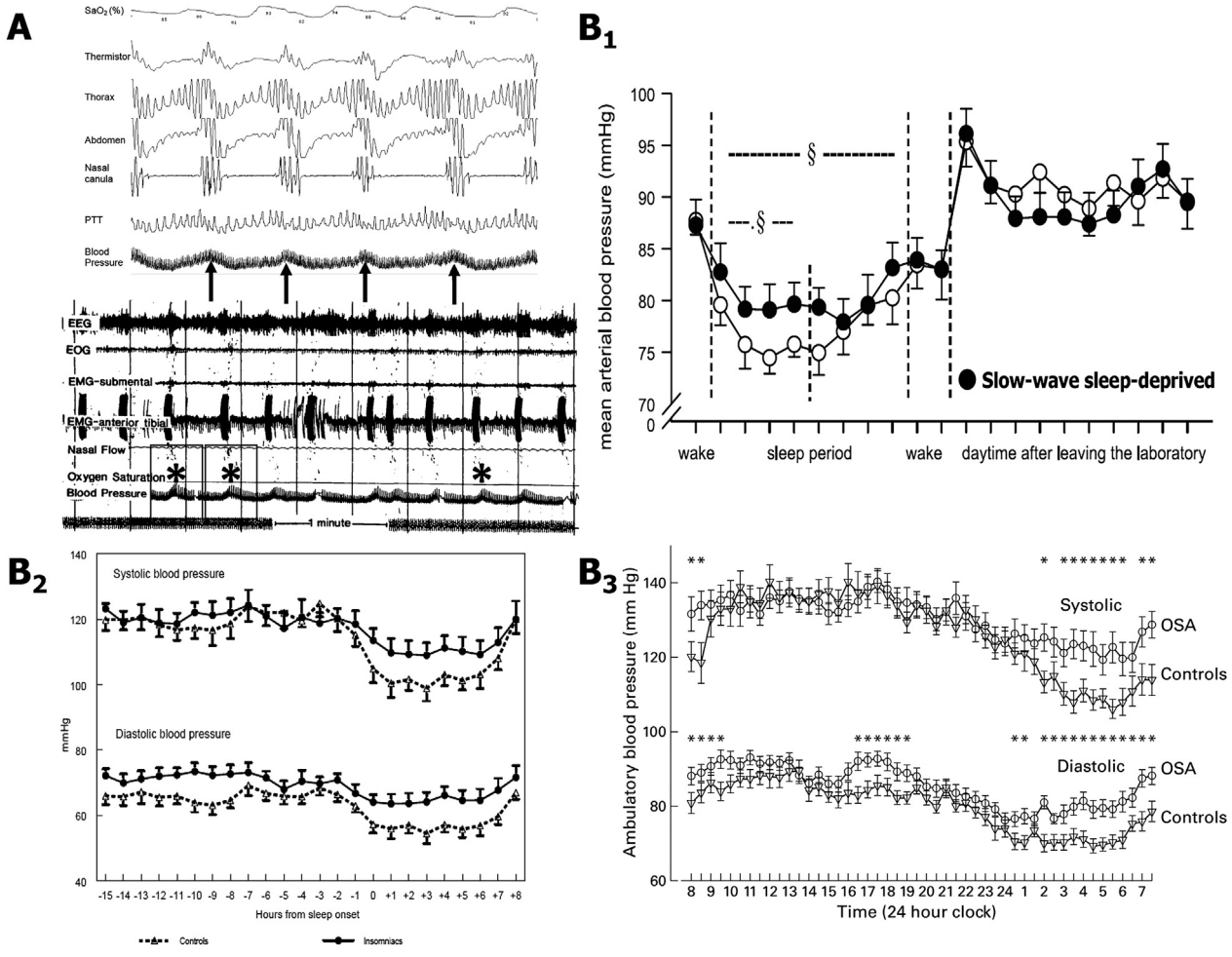

Fig. 2. Illustration of some of the mechanisms linking sleep, sleep disorders and hypertension. A – Acute surges in blood pressure associated with micro arousals induced by apneas (arrows) or periodic leg movements (*) (Modified from Ali et al. [89]). B – B_1: Acute sleep deprivation in normal subjects; B_2: reduction in total sleep time in insomnia; and B_3: sleep apnea (*),associated with a non-dipping pattern of blood pressure (Modified from Sayk F et al. [10], Lanfranchi PA et al. [60] and Davies R et al. [109]).

cohort studies, the sleep heart health study (SHHS) [51] and the national health and nutrition examination survey (NHNES) [52] were the first to report an association between self-reported sleep duration and hypertension. In the SHHS, Gottlieb et al. [51] found that the relationship between self-reported sleep duration and prevalent hypertension followed a U-shaped association. Indeed, in the 2813 men and 3097 women, aged 40–100 y, sleep duration above or below the median of 7–8 h per night was associated with an increased prevalence of hypertension. These associations remained after adjustment for potential confounders such as age, sex, race, obesity, apnea–hypopnea index or lifestyle habits. The same year, Gangwisch et al. [52] published results from a longitudinal analysis of the NHNES that reported an association between self-reported short sleep duration and incident hypertension. The study included 4810 men and women between 1982 and 1984. At this time, participants, aged between 25 and 74 y, were asked by questionnaire about their usual sleep duration. Their data regarding incident hypertension ($n = 647$) were then collected during the 8–10 y of follow-up. In comparison to self-reported sleep durations of 7–8 h, sleep durations of less than 5 h were found to be associated with incident hypertension in subjects younger than 60 y, whereas sleep durations of over 9 h per night were associated with incident hypertension in subjects older than 60 y, in adjusted analyses. Since these early reports, numerous population studies have assessed the relationship between sleep duration and hypertension. Most of these studies also used subjective, self-reported sleep duration; however, Knutson et al. [53], in an ancillary study of the coronary artery risk development in young adults (CARDIA) study, found a significant association between short sleep duration and prevalent as well as incident hypertension, using actimetry to obtain objective measurements of sleep duration. Moreover, a strong correlation has been observed between sleep timing and duration assessed subjectively by questionnaires and objectively by actimetry [54], suggesting that studies using only questionnaires are valid. However, the objective measurement of sleep duration remains the gold-standard when addressing the question of an authentic association with hypertension, and future studies should include such objective measurements in their design. The comparison of the different populations studied populations is also hampered by the heterogeneity of cut-offs used to define short or long sleep duration. The reference value for 'normal' sleep duration was 7–8 h per night in the majority of studies, whereas short sleep duration was defined either as below 7 h, 6 h or 5 h/night and long sleep duration above 8 h, 9 h or 10 h/per night.

The strength of the cross-sectional association between self-reported sleep duration and hypertension has been found to vary with age, gender [55] and geographic location. In a meta-analysis including 17 cross-sectional ($n = 105\,432$) and six longitudinal ($n = 9959$) studies, short sleep duration was associated with 20% increased risk of prevalent hypertension especially among subjects younger than 65 y and females [56]. In the Whitehall II Study, self-reported short sleep duration was associated with the increased prevalence and incidence of hypertension in women only [55]. In contrast, in the NHNES study self-reported short sleep duration was not found to be associated with incident hypertension in subjects aged between 60 and 86 y [52]. Likewise, hypertension was not associated with sleep duration assessed by either self-report or actigraphy in a cross-sectional study of 5058 'elderly' subjects, aged between 58 and 98 y, from the Rotterdam Study [57].

A recent systematic review and meta-analysis by Guo et al. [58] included 24 studies, 21 cross-sectional and six longitudinal. The studies included both men and women with ages ranging from 18 to106 y in North and South America, Europe, Asia and Australia. Pooled analyses of cross-sectional studies demonstrated a significant association between both short sleep duration, long sleep duration and prevalent hypertension (odds ratio (OR), 1.21; 95% CI 1.09–1.34; $p < 0.001$ and OR, 1.11; 95% CI, 1.04–1.18; $p = 0.003$, respectively), whereas longitudinal studies demonstrated an association only between short sleep duration and incident hypertension (relative risk, 1.23; 95% CI, 1.06–1.42; $p = 0.005$). However, in further analyses stratified by different population groups among the cross-sectional studies, short sleep duration was found to be associated with hypertension only among women (OR, 1.36; 95% CI, 1.17–1.57; $p < 0.001$). In contrast, men who slept longer had a greater risk of hypertension (OR, 1.12; 95% CI, 1.01–1.25; $p = 0.036$). No significant association between sleep duration and hypertension was observed in the European populations. Thus, while sleep duration seems to be associated with prevalent and incident hypertension, any causation cannot be proven by cross-sectional studies which are to date by far the majority compared to longitudinal studies. The reasons why such a relation seems to be more specific for females, younger age and to exclude the European population are not yet fully understood. NREM sleep forms a greater proportion of sleep in young people and females and could explain why the impact of restricted sleep is higher in these groups.

Haack et al. [59] hypothesized that increasing sleep duration may serve as an effective behavioral strategy to reduce BP. Subjects were randomized to a sleep extension group who aimed to increase the time spent in bed by 1 h daily over a 6-wk intervention period, or to a sleep maintenance group. Systolic and diastolic beat-to-beat BP averaged across the 24-h recording period significantly decreased from pre- to post-intervention in the sleep extension group by 14 ± 3 and 8 ± 3 mmHg respectively. They also noted that sleep extension was also associated with an increase in daily activity assessed objectively by actigraphy.

Insomnia

Short sleep duration and insomnia, although classically related, are different entities. Insomnia entails dissatisfaction with the quality of sleep and daytime consequences that can be explained or not by a true reduction in sleep duration. Individuals with short sleep duration do not necessarily suffer from insomnia since they can voluntarily restrict their sleep time. Insomnia is clearly related to psychiatric and psychosomatic disorders and some insomniac patients have a misperception of their sleep quality. Whether insomnia is associated with increased prevalence of somatic disorders, particularly cardiovascular ones, remains controversial. Recent studies have used polysomnography to show that insomnia with objective short sleep duration is associated with a significant risk of hypertension. In a study using 24-h beat-to-beat blood pressure recordings concurrently with polysomnography, it was found that normotensive subjects with chronic insomnia had higher nighttime systolic BP and blunted day-to-night systolic BP dipping compared to aged-matched good sleepers [60]. Vgontzas et al. [61] demonstrated, in a cross-sectional, population-based study, that insomnia was linked to prevalent hypertension only when insomnia was associated with objectively measured short sleep duration. The prevalence of hypertension increased 3.5 fold when sleep duration was between 5 and 6 h and 5.1-fold when sleep duration was below 5 h per night. Accordingly, chronic insomnia with short sleep duration (less than 6 h sleep during polysomnography) showed an increased risk of incident hypertension (odds ratio 3.8) in a general population sample of 786 adults in the Penn State Cohort without hypertension at baseline and followed for 7.5 y [62]. In middle-aged subjects in the NHNES, depression increased the incidence of hypertension, but the strength of this link was weakened by 33% after adjustment for

both sleep duration and insomnia, suggesting that these later conditions may, at least partly, mediate the relationship between depression and hypertension [63]. Overall, the link found between insomnia and prevalent or incident hypertension appears convincing when insomnia is associated with objective short sleep duration (<6 h/night). As only a small number of studies have directly addressed the question of the relationship between insomnia and hypertension, these results should be considered with caution.

Restless legs syndrome and periodic limb movement disorder

Restless legs syndrome (RLS) is characterized by dysesthesia and leg restlessness occurring predominantly at night during periods of immobility [64]. In the Wisconsin sleep cohort study, the prevalence of self-reported symptoms of RLS was 10.6% without differences between men and women [64]. Unpleasant sensations and the irresistible need to move impair the ability to fall asleep and sleep quality. RLS is associated in 80% of cases with periodic limb movements (PLMs), which are repetitive flexion of the lower limbs (hips, knees, ankles etc) whilst sleeping, sometimes ending in micro arousals. PLMs with or without micro arousals are characterized by abrupt increases in BP and surges in sympathetic activity (Fig. 2A). PLMs also occur in patients without RLS and are found in 25% of patients undergoing routine polysomnography, especially in those over 65 y.

Changes in sleep quantity and/or quality due to RLS has been suggested as being potentially associated with prevalent hypertension [65]. Among 4000 men aged 18–64 y in whom RLS was self-reported in questionnaires; Ulfberg et al. found that after adjustments for age, witnessed apnea, smoking, and alcohol consumption, RLS sufferers were more likely to report hypertension [66]. In a study by Ohayon et al. [67] including 18 980 individuals from five European countries, 732 met criteria for RLS and presented with a two-fold higher risk for elevated BP (21.8 vs. 11.1% for patients with and without RLS, respectively, for the association between hypertension and RLS after adjustment for confounders). Winkelman et al. [64], studying 2821 participants in the Wisconsin sleep cohort, found a higher prevalence of hypertension among patients having RLS, but the odds ratio for the cross-sectional association between RLS and hypertension was no longer significant after adjustment for confounding factors. A cross-sectional study including 65 544 women (aged 41–58 y), participating in the Nurses' health study II, demonstrated a dose–response relationship between RLS symptoms and values of systolic and diastolic BP [68]. Finally, a systematic review addressing the link between RLS and hypertension has identified 17 mainly cross-sectional studies from twelve countries [65]. In 13 studies, participant enrollment exceeded 1000 subjects. Ten out of the 17 studies supported a positive association between RLS and hypertension that persisted after adjustment for body mass index (BMI), smoking, and sleep problems. These somewhat inconsistent findings may be explained by variations in the studied populations, and by different ways of assessing hypertension and RLS. In addition, some medications used in the treatment of RLS can lower BP [65]. Collectively, these studies indicate that RLS might be positively related to hypertension when RLS symptom frequency is high, exceeding 15 d per month. However, causality based on these cross-sectional associations is not proven.

PLMs are associated with shifts in the sympatico-vagal balance during NREM sleep in adults [69] as well as in children [70] suggesting a potential impact on BP regulation. The studies addressing the question of comorbid conditions specifically associated with PLMs are tenuous and conducted in specific populations. A high PLM index has been shown as an independent predictor of higher cardiovascular risk in patients with chronic kidney disease [71]. In patients having RLS, those presenting with more than 35 periodic movements per hour had not a higher prevalence of hypertension, but had higher left ventricular hypertrophy which reflects sympathetic over-activity [72]. Accordingly, the combination of PLMs (>5 periodic movements/h) and OSA was not associated with a higher prevalence of hypertension, compared to patients having OSA without PLMs [73]. In summary, only a limited number of studies have addressed the specific relationship between PLMs and BP regulation or hypertension; and from the existing literature no clear conclusion can be drawn.

Narcolepsy–cataplexy

In narcolepsy–cataplexy (NC), the sleep–wake cycle is disrupted by the frequent occurrence of REM sleep episodes during the day and by numerous awakenings during the night [74,75]. The disease is characterized by a marked decrease of the number of hypocretin neurons which are known to play a role in central autonomic and cardiovascular regulation [76–78]. There are only few cardiovascular studies in patients with narcolepsy even though NC is classically associated with obesity, type 2 diabetes, and metabolic syndrome; all comorbidities increasing the cardiovascular risk. We have recently described the 24 h ABPM pattern of drug-free patients with narcolepsy compared to control subjects [79]. A "non-dipping status", defined as less than 10% drop in BP during sleep, was found in one third of the patients with NC and in only 4.8% of controls. The non-dipping diastolic condition was strongly associated with NC with an odds ratio up to 12-fold, and was significantly related to the percentage of REM sleep even after adjustment for confounders. In a small, case-controlled study using a 24-h beat by beat measurement of BP, Grimaldi et al. [80] have nicely demonstrated that systolic BP during night-time REM sleep was increased in the narcoleptic group. NC is therefore a unique example of increase in nocturnal BP occurring mainly during REM sleep. It is completely unknown whether this mechanistic pathway has specific implications regarding the risk of developing hypertension. PLMs and the sleep fragmentation that goes with it were also found associated with the loss of night-time dipping of BP in NC patients [80–81].

Thus, to date, only the loss of the nocturnal dipping pattern of BP, and not hypertension itself, has been demonstrated to be associated with NC. However, patients having NC will often be treated with psychostimulants for the rest of their lives. This therapy has a well-known deleterious impact on the autonomic nervous and cardiovascular systems. Thus the preliminary studies demonstrating an effect of NC on the BP dipping pattern might result in a significant clinical impact. Thus, further studies addressing the cross-sectional and longitudinal association between NC and hypertension as well as studies unto the mechanisms involved are clearly warranted.

Combinations of sleep problems

Only one population-based study, NHNES, has addressed the cross-sectional association between combinations of sleep problems and hypertension. This large study of 10 308 adult men and women, determined the odds ratios of having hypertension according to the self-reported presence of sleep disorders (sleep apnea, insomnia, RLS, and others), short sleep duration (<7 h/night), and "poor sleep" quality (one of the six following sleep problems occurring between 5 and 30 times a month: 1) trouble falling asleep; 2) waking up during the night and having trouble getting back to sleep; 3) waking up too early in the morning and being unable to get back to sleep; 4) feeling unrested during the day, no

matter how many hours of sleep were obtained; 5) feeling excessively or overly sleepy during the day; and 6) not getting enough sleep); or any combination of sleep disorders, short sleep duration and poor sleep. Having a single sleep disorder was not significantly associated with hypertension (OR 1.65; 95% CI 0.73–3.77), but the combination of sleep disorders and short sleep (OR 2.30; 95% CI 1.49–3.56) and of sleep disorders, short sleep and poor sleep (OR 1.84; 95% CI 1.13–2.98) were significantly linked with hypertension [82].

Another study with a case–control design compared sleep patterns in patients having OSA and either resistant hypertension, controlled hypertension or no hypertension. Subjects with resistant hypertension had shorter total and REM sleep times and lower sleep efficiency than the others, demonstrating that a combination of OSA and objective short sleep duration act synergistically to worsen hypertension [83].

Owing to the high prevalence of each sleep problem, it is expected that a combination of sleep problems would be frequent. For instance, a high prevalence (39%–58%) of insomnia symptoms have been reported in patients with OSA, and between 29% and 67% of patients with insomnia have an apnea–hypopnea index greater than 5 per hour [84], whereas combined OSA and RLS were found in 44% of patients [73]. One can hypothesize that the cumulative impact of two or more sleep disorders or sleep problems could be associated with a greater risk of a non-dipping pattern and secondary hypertension. This is clearly a new area of research with a potentially important clinical impact.

Common intermediary mechanisms for the link between sleep habits, sleep disorders and hypertension (Fig. 3)

There is strong evidence for a relationship between OSA and prevalent as well as incident hypertension. The impact of CPAP therapy on the development and control of hypertension in OSA patients is significant but of limited amplitude. In population studies, short sleep duration as well as long sleep duration is associated with an increased risk of hypertension. However, the quality of evidence suffers from the shortcomings of the studies, mainly the use of self-reported sleep duration and variable cut-offs to define short and long sleep duration. The link between short sleep duration and hypertension seems to be more specific to women than to men, occurs more frequently in subjects below 60 compared to subjects above 60 y-old, and varies according to geographic location and ethnic origin. However, most of sleep deprivation studies have demonstrated an acute impact on BP that sustains the hypothesis that chronic short sleep duration may be deleterious for BP control. Finally, sleep disorders like RLS/PLMs and narcolepsy might affect BP control, but our current knowledge is based on relatively few population/experimental or mechanistic studies, pleading for more studies to address the question of the relationship between these diseases and hypertension.

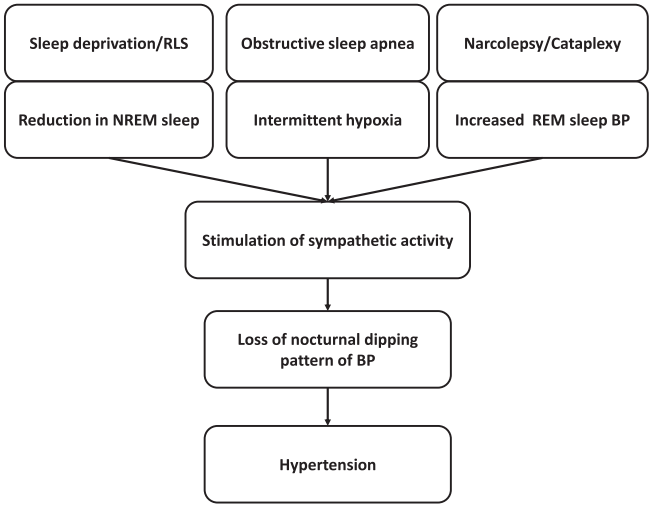

Fig. 3. The common intermediary mechanisms for the link between sleep, sleep disorders and hypertension. Abbreviations: blood pressure (BP), hypothalamic–pituitary–adrenal (HPA), non-rapid eye movement (NREM), rapid eye movement (REM) restless legs syndrome (RLS).

Causality between sleep problems and the development of hypertension has been strongly demonstrated only in OSA, with more tenuous evidence for sleep duration. The common hypothesis connecting sleep disorders or poor sleep habits to the development of hypertension is that alterations in sleep quality/quantity lead to the loss of the nocturnal dip in BP that is associated with NREM sleep as the first step toward the hypertension disease. Loss of the BP dipping pattern is mainly attributable to an increase in nocturnal sympathetic activity, which in turn leads to a diurnally permanent increase in sympathetic tone. Indeed, OSA is associated with increased levels of urinary catecholamines [85-86] and increased muscle sympathetic nerve activity that are both lowered by CPAP treatment [87]. Sleep deprivation has also been shown to increase sympathetic tone [43–45,88] and PLMs induce a surge in BP due to an acute rise in sympathetic activity [89]. Besides changes in catecholamine levels, the levels of other hormones with vasoactive effects are impacted by sleep problems. Angiotensin II and aldosterone are increased in OSA patients compared to controls [90]. In addition, because nocturnal awakenings have been associated with pulsatile cortisol release [90], OSA would be expected to activate the hypothalamic–pituitary–adrenal (HPA) axis. Several studies have addressed this question and were recently reviewed by Tomfohr et al. [91]; however, the heterogeneity of the studies did not allow pooling of the results for meta-analysis. Mixed results have been found concerning cortisol levels in OSA patients compared to controls, when the effects of CPAP treatment on cortisol levels are looked at. Such discrepancies may be attributable to methodological biases such as infrequent sampling and inconsistent timing of sample collection. However, two recent studies [92,93] have collected multiple measurements of cortisol via venous blood sampling over a 24-h period pre and post treatment with 3-mo of CPAP. Henley et al. [93] sampled blood at 10-min intervals over 24-h in 10 men newly diagnosed with mostly severe OSA. They found that cortisol levels were in general reduced after 3-months of CPAP therapy. Vgontzas et al. [92] sampled blood at 30-min intervals over 24-h in obese patients without OSA, in obese patients with OSA and in non-obese controls. The highest 24-h cortisol levels were found in the non-obese controls, whereas obese men with OSA had higher cortisol levels than obese men without OSA. They also found a trend towards an overall reduction in 24-h cortisol levels after 3-mo of CPAP treatment. Besides these mixed results regarding OSA effects on the HPA axis, sleep deprivation was also found to be linked with an increase in HPA axis activity [88]. In 17 young adults with chronic insomnia, 24-h urinary free cortisol levels were positively correlated with total time spent awake [94]. These results were later confirmed in two controlled studies conducted in a dozen patients: Adrenocorticotrophic hormone (ACTH) and cortisol secretions were significantly higher in young men and women with insomnia, compared with non-insomniac controls [95,96], whereas another study found no difference in cortisol levels but a decrease in melatonin secretion in patients with insomnia compared to control patients [97]. Rodenbeck et al. [98] conducted a cross-over study addressing the effects of the tricyclic antidepressant doxepin on nocturnal sleep and plasma cortisol concentration in ten patients with chronic primary

insomnia. The antidepressant treatment improved sleep significantly and reduced mean cortisol levels. Overall, these results suggest a cross-sectional association between insomnia and activation of the HPA axis, whereas the nature of the relationship (causation or consequence) cannot be clarified from these studies.

Inflammation, oxidative stress and endothelial dysfunction are also linked with sleep quantity, sleep disorders [99–101] and may influence the development and progression of hypertension. For instance, 20 normal sleepers subjected to one week of moderate sleep deprivation (from 8 h/night to 6 h/night) showed an increase in 24 h-interleukin-6 (IL-6) levels (men and women) and in 24 h-tumor necrosis factor (TNF)-alpha levels (men only) [102]. Laboratory studies with more drastic sleep deprivation (4-h/night) also demonstrated an increase in plasma IL-6 and urinary levels of prostaglandin metabolites D2 and E2 after sleep deprivation [103,104].

Increased sympathetic activity (and activation of the HPA axis, but with less robust evidence) seems to drive the impact of OSA on BP. Sympathetic activity is also increased in sleep deprivation, RLS and NC. However, these conditions have different pathophysiologies and lead to increased sympathetic activity through different pathways. In the OSA-associated increase in sympathetic activity, the role of intermittent hypoxia seems prominent. Indeed, both in animal models submitted exclusively to intermittent hypoxia [105] and in healthy human volunteers submitted to intermittent hypoxia in a "tent" that we developed [106], intermittent hypoxia was able to increase sympathetic tone. During the night abnormal respiratory events, increased sympathetic activity and acute rises in BP correlate with the severity of oxygen desaturation (Fig. 2A). Respiratory event-related intermittent hypoxia is the main stimulus leading to over-activity of the adrenergic and renin–angiotensin systems.

Sleep deprivation is of course not associated with intermittent hypoxia; however, an increase in sympathetic activity is observed that might be the consequence of the reduction of time spent in NREM sleep. A selective deprivation in slow wave sleep is associated with a reduction in the amplitude of the nocturnal dip in BP [10], supporting the hypothesis that disturbed NREM sleep quantity or quality might be the mechanism by which sleep deprivation or RLS lead to an increase in sympathetic tone. Conversely, the particularity of the abnormal nocturnal BP pattern in NC could be partially related to the increase in BP during REM sleep [80].

Perspectives

There is a substantial connection between the nocturnal profile of BP, hypertension and sleep problems, either because of a causal relationship (as demonstrated in OSA, in short and long sleep duration), or because sleep problems and hypertension are frequently comorbid owing to their shared risk factors (obesity, excess visceral adiposity). Thus, the diagnosis of one of these conditions (either a sleep-related disorder, detrimental sleep habits or hypertension) should alert the physician to the possibility of the other, calling for multidisciplinary collaboration between cardiologists and sleep specialists.

To date,far, the body of literature has extensively reported on the relationship between OSA and hypertension with several convincing interventional studies. Regarding the duration of sleep, numerous population studies have permitted to nuance the strength of the relationship with hypertension according to subgroup of the general population. Very few intervention studies have been realized that advocate r for more studies on sleep extension (or sleep reduction for long sleepers). Considering RLS, several cross-sectional studies have brought contradictory results without any longitudinal study. Studies addressing the potential link between NC and abnormal BP profile are scarce and complementary mechanistic studies are also needed.

Conclusions

In hypertension, sleep quality is of importance. Sleep problems should be addressed in their diversity, including poor sleep habits, sleep breathing disorders, RLS, PLMs, NC and combinations of conditions acting synergistically to adversely affect BP control. There is a need for more collaborative work between cardiologists and sleep specialists, both in a clinical context as well as in research.

Practice points

1) The nocturnal blood pressure profile is altered in obstructive sleep apnea syndrome leading to secondary hypertension. Sleep apnea treatments decrease the incidence of hypertension and produce a small reduction in mean blood pressure.
2) Sleep durations that are shorter or longer than normal may increase the incidence of hypertension; however, this seems to be dependent of age, gender, geographic location and ethnic origin.
3) Preliminary studies suggest that restless legs syndrome and narcolepsy–cataplexy may adversely affect nocturnal blood pressure control.
4) Poor sleep habits and sleep disorders should be considered by the cardiologist in the initial evaluation of secondary hypertension, bearing in mind that several sleep problems together could have a synergistic effect on blood pressure.

Research agenda

1) As the first phase of a sleep-related increase in blood pressure appears in the nocturnal blood pressure profile, 24-h ambulatory blood pressure monitoring should be used as the method of reference for blood pressure measurement in future studies.
2) Most of studies addressing the role of sleep duration have used self-reported sleep duration and a variety of cut-offs to define short or long sleep duration. Actigraphy should be used more systematically to assess sleep duration.
3) The association between restless legs syndrome and prevalent hypertension seen in the available cross-sectional studies showed contradictory results. There is a need for longitudinal and interventional studies in this area, as well as for patients with narcolepsy–cataplexy.
4) The effects of combined sleep problems (either detrimental sleep habits or sleep disorders) should be addressed in the future, particularly regarding their potential synergistic impact on the incidence of hypertension.

Conflict of interest

None.

Acknowledgments

Conseil scientifique «Agiradom».

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